The Rise and Fall of Aspirin in the Primary Prevention of Cardiovascular Disease

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Abstract

Aspirin is one of the most frequently used drugs worldwide and is generally considered effective for the secondary prevention of cardiovascular disease (CVD). In contrast, the role of aspirin in primary prevention of CVD is controversial. Early trials evaluating aspirin for primary prevention, conducted before the turn of the millennium, suggested possible reductions in MI and stroke, although not mortality, and an increased risk of bleeding. In an effort to balance the risks and benefits of aspirin, international guidelines on primary prevention of CVD have typically recommended aspirin only when there is a substantial 10-year risk of CV events. However, recent, large randomized clinical trials of aspirin for the primary prevention of CVD demonstrate little or no benefit and possible harm. In this narrative review, we reappraise the role of aspirin in primary prevention of CVD contextualizing data from historical and contemporary trials.

Introduction

Extracted from willow bark, salicylates were first used as an analgesic by the ancient Sumerians and Egyptians.[1] Later civilizations found salicylates to be an effective treatment for pain, inflammation, and fever; however, their use was limited by gastric side effects. Under the instruction of Arthur Eichengrun, the German chemist Felix Hoffmann discovered that incorporation of an acetyl group to salicylic acid reduces its propensity for gastric irritation, resulting in the first production of acetylsalicylic acid, known more commonly as aspirin, in 1897 (**Figure**).[2]

Almost a century later, in 1974, a randomized controlled trial showed a non-significant reduction in deaths amongst patients with a recent myocardial infarction (MI) who were assigned to aspirin 330mg/day.[3] This launched a series of trials that resulted in widespread acceptance of aspirin for the secondary prevention of major adverse cardiovascular events (MACE).[4–11] Enthusiasm for aspirin led to further randomized controlled trials investigating whether aspirin might be effective for the primary prevention of cardiovascular disease (CVD).[12–17] Several primary prevention trials, mostly conducted before the turn of the millennium, suggested reduction in MI and stroke, although not mortality[16], and at a cost of increased bleeding events.[12–15] These findings influenced guidelines, which recommended prescribing aspirin for primary CVD prevention in high-risk individuals.[18–20] Aspirin is now one of the most widely used medications. In the U.S. alone, it is estimated that 35.8 million adults are taking aspirin for the primary prevention of CVD, often without consulting their physicians.[23]

Despite aspirin's popularity, its use for the primary prevention of CVD is controversial. Indeed, the U.S. Food and Drug Administration (FDA) has never approved the labeling of aspirin for this purpose. The European Medicines Agency (EMA) have not addressed this

question. Furthermore, recent clinical trial data have placed the utility of aspirin for the primary prevention of CVD back under scrutiny due to their neutral results[24,25] or evidence of harm.[26] In this article, we summarize the mechanism of action, review historical and contemporary trials evaluating aspirin, and reflect on future directions for aspirin in the prevention of CVD.

Search Strategy and Selection Criteria

PubMed was used to identify relevant references using the search terms "aspirin", and "primary prevention". We also searched all of the references in recent systematic reviews and metanalyses on this topic.[27–29] Only articles published in English between January 1970 and January 2019 were included in this narrative review.

Mechanism of Action

Acetylsalicylic acid binds to and irreversibly inhibits cyclooxygenase (COX), which exists as two isoforms in humans: COX-1 and COX-2.[30] COX-1 is involved in platelet aggregation through production of thromboxanes. COX-2 is involved in the upregulation of prostaglandins that have vasodilator and anti-aggregatory actions.[31] Both isoenzymes are associated with protection of the gastric mucosa.[32] In experimental settings, low dose aspirin (75 mg or 81 mg) inhibits COX-1 and disrupts the production of thromboxane A_2[33] thereby reducing platelet aggregation and formation of thrombus.[34] Higher aspirin doses inhibit COX-2[35] leading to reduced production of prostacyclin and prostaglandin-E, which is responsible for aspirin's analgesic and antipyretic effects but may cause vasoconstriction, renal dysfunction, hyponatremia, and pro-aggregatory effects.[36] For patients with cardiovascular disease, doses of aspirin as low as 75mg/day may suffice to block both systems for 24 hours or more.

Trials of Aspirin for Primary Prevention Before 2000

Non-targeted populations

The first primary prevention trials investigating the utility of aspirin in preventing MI enrolled physicians, as was not uncommon at the time **(Table 1).** The British Male Doctors Trial randomized 5,139 men aged <80 years, 10-15% of whom had a prior history of non-MI cardiovascular disease, to 300-500 mg aspirin/day or no aspirin (unblinded).[13,17] After a six-year follow up, there were no differences in the incidence of or mortality from stroke, MI, or other CVD. Importantly, the rates of non-fatal and fatal MI were similar, with sudden death notably included in the fatal MI endpoint. [17]

The US Physicians' Health Study enrolled 22,071 healthy male physicians aged 40-84 years and randomized them, double-blind, to aspirin 325 mg every other day or placebo.[13] The trial was stopped for futility by the data monitoring committee during an interim analysis because only 88 of the expected 733 cardiovascular deaths had occurred within the first 4.8 years of follow-up and because of an observed reduction in non-fatal and fatal MI, a key secondary endpoint. In the final report with full follow-up for events, the investigators found a 44% reduction in the rate of non-fatal and fatal MI in those assigned to aspirin (255 vs 440 per 100,000 per year; $p<0.00001$). There was no reduction in angina, stroke, cardiovascular death, or all-cause mortality. The ratio of fatal to non-fatal MI was dramatically different in the British and US trials (ratio of ~1.0 in British and ~0.1 in US trials). The aspirin group had higher rates of bleeding [relative risk (RR) 1.32; 95% CI 1.25-1.40; $p<0.00001$] and were more likely to require a blood transfusion (RR 1.71; 95% CI 1.09-2.69; $p=0.02$).[13] The early termination of the US trial for a reduction in a secondary endpoint, differences in population risk, and differences in the definition or ascertainment of MI may account for the divergent results found in the two trials.

Targeted populations with cardiovascular co-morbidities

Subsequent studies shifted the focus to lower doses of aspirin and higher-risk groups for CVD, such as patients with hypertension and diabetes mellitus (DM). The Primary Prevention Project randomized 4,495 men and women with one or more cardiovascular risk factors to 100 mg/day aspirin or no aspirin without blinding.[14] The trial terminated early at the second interim analysis, again despite no difference in the pre-specified primary outcome, after a median follow-up of 4 years demonstrated a 44% reduction in cardiovascular death (RR 0.56; 95% CI 0.31-0.99) and 23% reduction in total cardiovascular events (RR 0.77; 95% CI 0.62-0.95) with aspirin. There was no significant treatment effect on all-cause mortality, and there was also an increased rate of severe bleeding in the aspirin group (1.1% vs 0.3%; $p<0.0008$). Similarly, the Thrombosis Prevention Trial (TPT) found that men at high-risk for MI who received aspirin had a 32% reduction in nonfatal MI ($p=0.004$) over a 6.8-year median follow up. This effect was largely driven by the combination of aspirin with warfarin.[12] Aspirin alone did not significantly reduce the primary endpoint of fatal or nonfatal MI compared to placebo. There was also no change in cardiovascular or non-cardiovascular death.

In the Hypertension Optimal Treatment (HOT) Study,[15] researchers found a 15% risk reduction in the primary endpoint of major cardiovascular events (RR 0.85; 95% CI 0.73-0.99; $p=0.03$) and a 36% reduction in patient hospitalized with MI (RR 0.64; 95% CI 0.49-0.85, $p=0.002$) at 3.8-year mean follow-up. However, there were more silent MI events on aspirin (73) than placebo (57), which would have rendered the trial neutral had they been included in the primary endpoint. Furthermore, the inclusion of a number of patients with prior MI, stroke, and other CVD may have confounded the results of this trial from a primary prevention perspective;

though the authors reported no major difference in the effect of aspirin between the secondary prevention group and the general study population.

Influence of Sex

The Women's Health Study (WHS) randomized 39,876 women to 100 mg aspirin on alternate days versus placebo.[16] The primary endpoint of the trial was not met. Although there was a 17% reduction in stroke (RR 0.83; 95% CI 0.69-0.99; p=0.04), there was no change in the rates of MI or cardiovascular death over a mean follow up of 10.1 years. While subgroup analyses from the early trials and early meta-analyses suggested different effects of aspirin on men and women,[37,38] the 2009 Anti-Thrombotic Trials Collaboration metanalysis of six primary prevention trials found no sex-stratified differences when correcting for multiple testing.[39]

Trials of Aspirin for Primary Prevention 2000 to 2017

Major advances in cardiovascular risk reduction have been implemented in the last 20 years, including marked reductions in tobacco smoking,[40,41] widespread evidence-based prescribing of statin therapy[42], and improved population control of blood pressure[43]. Thus, the turn of the millennium brought about a reappraisal of aspirin's safety and efficacy for the primary prevention of CVD **(Table 2).** Furthermore, the publication of a universal definition of MI and advances in the utilization of cardiac biomarkers, including more sensitive measures like troponin,[44,45] improved the consistency of determining endpoints such as MI.

Patients with Diabetes Mellitus

Several contemporary trials have focused on patients with DM. The Prevention of Progression of Arterial Disease and Diabetes (POPADAD) trial enrolled 1,276 patients aged ≥40 years with type 1 or type 2 DM and an ankle-brachial pressure index of 0.99 or less but no symptomatic

CVD, to receive aspirin 100 mg daily or placebo. Aspirin did not reduce the primary composite endpoint of cardiovascular death, non-fatal MI, stroke, or amputation for critical limb ischemia (RR 0.98; 95% CI 0.76-1.26) or the rate of non-fatal MI alone.[46] Similarly, the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) trial, which enrolled patients with type 2 DM aged 30 to 85 years, found that aspirin at a dose of 81 mg or 100 mg daily did not significantly reduce a composite outcome of atherosclerotic events at 4.4 years follow-up (RR 0.80; 95% CI 0.58-1.10; $p = 0.16$).[47]

Patients with Other Cardiovascular Co-morbidities

The Aspirin for Asymptomatic Atherosclerosis Trial (AAA) enrolled 3,350 men and women aged 50 to 75 years with low ankle-brachial index and no history of CVD. The trial was neutral for its primary endpoint, a composite of fatal or nonfatal coronary events, stroke, or revascularization (RR 1.03; 95% CI 0.84-1.27) and for all-cause mortality (RR 0.95; 95% CI 0.77-1.16) over a mean follow up of 8.2 years.[48] The Japanese Primary Prevention Project (JPPP) randomized 14,464 subjects aged 60-85 with multiple cardiovascular risk factors to aspirin 100 mg daily or not (unblinded). The study was stopped early for futility on its composite outcome of cardiovascular death, nonfatal stroke, and nonfatal myocardial infarction, although a reduction in non-fatal MI was observed (RR 0.53; 95% CI 0.31-0.91; p=0.02). An increase in extra-cranial hemorrhage requiring transfusion or hospitalization (RR 1.85; 95% CI 1.22-2.81; p=0.004) was also observed.[49]

Trials of Aspirin for Primary Prevention in 2018

The ARRIVE (Aspirin to Reduce Risk of Initial Vascular Events) trial randomized 12,546 men (aged ≥55) and women (aged ≥60) with moderate CVD risk (defined as a 10-year risk of

coronary heart disease of 10-20%) to 100 mg aspirin versus placebo.[24] The primary endpoint, a composite of cardiovascular death, MI, unstable angina, stroke, or transient ischemic attack, was neutral (RR 0.96; 95% CI 0.81–1.13; p=0.60) and there was no difference in non-fatal MI. Gastrointestinal bleeding was higher in the aspirin group (RR 2.11; 95% CI 1.36–3.28; p=0.0007), but the rates of intracranial hemorrhage were similar (0.13% vs 0.18%). The study population included patients with high blood pressure (63%), cigarette use (29%), and high LDL (44%). While the estimated risk of CVD in the study population calculated based on risk scores was 17.3%, the event rates of cardiovascular disease were much lower than expected (less than 10% over 10 years). The lower than anticipated event rates perhaps reflects the benefits of contemporary CVD preventive therapies.

The ASCEND (A Study of Cardiovascular Events in Diabetes) trial randomized 15,480 subjects to aspirin or placebo.[25] The study had a population with higher BMI, greater proportion of men, though lower proportion of smokers compared with the previous studies of prophylactic aspirin in diabetes. A 12% reduction in non-fatal vascular events with aspirin (RR 0.88; 95% CI 0.79-0.97; p=0.01) was observed, but at an increased risk of major bleeding (RR 1.29; 95% CI 1.09-1.52; p=0.003). The incidence of fatal bleeding (0.2 % vs. 0.2%) and hemorrhagic stroke (0.3% vs. 0.3%) did not differ between groups. There was no reduction in hard endpoints such as vascular death. During the course of the trial, due to lower than expected event rates, the Steering Committee added transient ischemic events to the primary composite endpoint, extended the study duration, and expanded the sample size. The large sample size enabled the detection of the relatively small absolute risk reduction of 1.1% in the efficacy endpoint. However, this must be weighed against the increased absolute risk of major bleeding of 0.9% and the lack of effect on CV or all-cause mortality.

The most recent and largest of the contemporary trials examined the utility of aspirin among older patients. The ASPREE (Aspirin in Reducing Events in the Elderly) trial randomized 19,114 health patients aged 70 years or older (≥65 years of age for Blacks and Hispanics) to aspirin 100 mg daily or placebo.[26] At a median follow-up of 4.7 years, there was no difference in CV events, including fatal and nonfatal MI and stroke between the two groups (RR 0.95; 95% CI 0.83-1.08).[26] However, an increased in the risk of intra- and extra-cranial hemorrhage (RR 1.38; 95% CI 1.18-1.62; p<0.001) and all-cause mortality (RR 1.14; 95% CI 1.01-1.29) was reported.[26,50] The trial also showed no reduction in the primary endpoint, a composite of dementia, death, or persistent physical disability,[51] which may be more important to some patients than the cardiovascular endpoints assessed, though is notably a heterogenous endpoint less likely to have been influenced by aspirin therapy.

Certain limitations of the 2018 trials can contribute to their null results. First, in all 3 of the 2018 aspirin trials, compliance with random assignment to aspirin was relatively poor, at 60-70%, resulting in significant cross-overs that might have influenced the null results. Second, the populations studied had lower than anticipated cardiovascular risk, which leaves unanswered the question of whether aspirin has benefit in higher risk populations. Third, only a small proportion of patients were treated with proton pump inhibitors, an intervention which may have improved rates of gastrointestinal bleeding in the aspirin arm. Fourth, there was a lack of information regarding the use of NSAIDs and alcohol which may increase bleeding risk. Fifth, the median follow-up time ranged 4.7-7.4 years which may be too short to appreciate primary preventative effects in cardiovascular disease. Finally, the 2018 trials did not provide information on modern risk stratification modalities such as coronary calcium score.

Contemporary meta-analyses

A recent meta-analysis of 11 primary prevention aspirin trials with 157,248 individuals, reported in early 2019, found no reduction in all-cause mortality overall or amongst patients with diabetes or high CV risk.[27] There was, however, an increase in the absolute risk of major bleeding by 0.6% and intracranial hemorrhage by 0.1%.[27] The aggregate analysis of all trials found a reduction in MI with aspirin use (RR=0.82, 95% CI 0.71–0.94, p=0.006). However, this reduction was no longer significant when only the more contemporary trials reporting after the year 2000 were included (RR=0.90, 95% CI 0.79–1.02, p=0.10).

Another recent metanalysis included 13 trials with 164,225 participants.[28] Aspirin reduced the composite outcome of cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke (RR=0.89, 95% CI 0.84-0.95) with an absolute risk reduction of 0.38% (number needed to treat 265). There was no difference in all-cause or CV mortality. There was an increased rate of major bleeding events (RR=1.43, 95% CI 1.30-1.56) with an absolute risk increase of 0.47% (number needed to harm 210). Again, this analysis showed less benefit in more recent trials, including no significant effect on MI, although a modest reduction persisted in the composite cardiovascular outcome (RR=0.90, 95% CI 0.83-0.98).

Can the Discordance between Older and Newer Aspirin Trials be Harmonized?

While some might reasonably argue that aspirin has never been conclusively shown to be efficacious in primary CVD prevention, most would agree that any potential benefits of aspirin for this indication (specifically reductions in non-fatal CVD) are much less evident in contemporary trials than before. How can this apparent change in effect of aspirin on reducing non-fatal MI and stroke in primary prevention be explained? One of the leading hypotheses is that improved control of CVD risk factors, including smoking, hypertension and hyperlipidemia,

has rendered aspirin for primary prevention obsolete.[52] This is certainly possible; aspirin is not known directly to inhibit atherogenesis or stabilize plaque nor does it specifically target any primordial risk factor for CVD. Rather, the presumed benefit of aspirin for primary prevention is to abort an impending or subclinical MI from becoming a manifest clinical MI by inhibiting platelet coagulation. Indeed, there is some evidence that most MIs are small and subclinical and that spontaneous lysis of a forming clot regularly aborts these before clinical manifestations occur, even without aspirin.[53,54] However, if less of these subclinical MIs are happening because of improved control of causal risk factors for atherosclerosis (e.g., tobacco, inflammation, hypertension, hyperlipidemia, dysglycemia), then the role of aspirin will become less relevant and, eventually, perhaps even obsolete for primary prevention.

The hypothesis that improved control of underlying CVD risk factors explains aspirin's diminishing benefit in primary prevention can be examined. Based on our review of the major trials to date (**Tables 1 and 2**), we compared risk factor burden and prevalence of preventive treatments among participants of trials before and after 2000 **(Table 3).** It is important to note that contemporary trials sought to select study populations with high cardiovascular risk, such as patients with DM (e.g., POPADAD, JPAD, ASCEND) or multiple cardiovascular risk factors (ARRIVE). Ultimately, ARRIVE trial had lower than expected event rates of cardiovascular disease (less than 10% over 10 years) and therefore it may not capture aspirin's effect on a higher risk population. Similarly, the ASCEND trial had a small percentage of patients (17%) with high estimated cardiovascular risk.

To understand whether contemporary care may have impacted on the discordant results between historical and recent trials, we compared the cardiovascular risk factors present in the study populations of these trials. The weighted-average of mean systolic blood pressure (140

mmHg vs 157 mmHg), tobacco use rate (13.9% vs 15.6%), and mean total cholesterol [5.0 mmol/L (193 mg/dl) vs 6.1 mmol/L (235mg/dl)] were all lower in trials reported after the year 2000 but there was more obesity (body mass index 27.7 vs 26.9) and higher rates of DM (38.4% vs 4.4%) even when trials on diabetic patients were excluded (14% vs 4.4%). Statin use was generally not reported in the early aspirin prevention trials and was presumably very low. The first FDA approval of a statin therapy was not until 1987 and landmark randomized trials reporting the utility of statins in primary cardiovascular prevention did not report until the late 1990s and 2000s.[55,56] With the available data, however, it does appear statin use was markedly higher in the later aspirin primary prevention trials (47% vs 16%). It is possible that the greater use of statin therapy, and improvements in blood pressure control and smoking cessation, in more recent trials may have reduced the risk of plaque rupture events thus limiting the opportunity for aspirin to prevent major clinical events.

Another potential explanation is that revisions of the definition of MI and the use of more sensitive cardiac biomarkers have reduced the reported benefit of aspirin in contemporary trials. The endpoint of non-fatal MI, in particular, is worth examining closely, as this is the endpoint that was most consistently improved in earlier aspirin trials **(Table 4)**. The early trials utilized World Health Organization definitions of MI from the 1970s[57,58] which explicitly did not include a standardized type or level of cardiac biomarker to categorize MI, as there was not enough data at the time to support endorsement of a particular laboratory test. As such, objective cardiac biomarker elevations were not required for the diagnosis of MI in many of the older trials.[59] In the absence of cardiac-specific biomarkers, these early definitions of MI could be mimicked by pulmonary, gastrointestinal, or musculoskeletal disease which would confound the clinical endpoint assessed in the trials. Furthermore, the lack of sensitive biomarkers meant that larger

MIs (such as those evident on ECG) were more likely to be detected than smaller MIs in these early trials.

Newer MI definitions developed by the American Heart Association,[60] American College of Cardiology,[61] and European Society of Cardiology[61,62] subsequently began to incorporate novel biomarkers more specific to cardiac damage such as CK-MB and troponin. The later aspirin trials adopted these contemporary definitions of MI. These differing criteria, and ability of recent trials to detect smaller MIs, might explain in part the discrepancy between older and more contemporary aspirin trials. One hypothesis is that the effect of aspirin on MI prevention may depend on how large the MI is. Potentially aspirin can prevent an evolving MI from becoming large enough to be diagnosed using older criteria, but may have less effect in preventing small plaque rupture events detectable by sensitive cardiac biomarkers.[63]

This hypothesis (that aspirin might modify the presentation but not prevent MI) is consistent with the increased proportion of 'silent' MIs recorded in the aspirin arm of the HOT trial versus the placebo arm (48% vs 31% of all MIs were silent in the aspirin vs placebo arms).[15] This suggests that aspirin may be responsible for converting otherwise clinically manifest (or 'noisy') MIs to silent ones. Because silent MIs appear to have similar prognostic implications to non-fatal MIs that are not silent,[64,65] this might help to explain the consistent lack of benefit for aspirin on CVD death or all-cause mortality. More contemporary trials using highly sensitive cardiac biomarkers may also be subject to more 'noise' in the MI endpoint (e.g., some troponin elevations in more recent trials may reflect myocardial injury and not true type 1 MI), which could also explain the diminishing benefit for aspirin evident in trials using modern biomarkers. Despite the above arguments, any effective treatment for the prevention of MI should theoretically reduce downstream morbidity (e.g., heart failure) and death. While the lack of

benefit for fatal CVD in updated meta-analyses of primary prevention aspirin appears to confirm a diminishing effect of aspirin in recent trials, it is also true that case-fatality from MI has fallen in modern studies[66,67] and that the relatively short follow-up of recent trials (typically <5 years on average) means that extended follow-up of these studies will be important to report.

Current Guidelines

Guidelines on the prophylactic use of aspirin to prevent CVD vary internationally but have become more conservative in recent years **(Table 5)**. The 2016 European Society of Cardiology (ESC) primary prevention guideline recommends against initiating aspirin in individuals without overt cardiovascular disease.[68] This was a downgrade from the 2007 ESC guideline which stated aspirin could be considered when the 10-year risk of cardiovascular mortality was substantial (SCORE risk>10%) and blood pressure was controlled.[19] In contrast to current European recommendations, the 2016 United States Preventative Services Task Force (USPSTF) guideline recommends aspirin for patients aged 50-59 with a 10% or greater 10-year CVD risk and a low risk of bleeding (Grade B recommendation) but it is less enthusiastic for patients aged 60-69 and recommends an individualized decision regarding aspirin use.[18] The 2015 American Heart Disease/American Diabetes Association (AHA/ADA) guidelines recommend low-dose aspirin for patients with diabetes who have a 10-year CVD risk of at least 10% but are not at increased risk of bleeding (Class IIa). They state low-dose aspirin is a reasonable choice for adults who have DM and a 10-year CVD risk between 5% and 10% (Class IIb).[69] An updated joint AHA and American College of Cardiology guideline will be released in March 2019.

Conclusion/Future Directions:

These new trials argue for a major change in how we prescribe aspirin for the prophylaxis of CVD. However, one caveat is that there remains a signal, albeit inconsistent, that aspirin might reduce non-fatal MI (e.g., this was evident in ASCEND and in the on-treatment analyses of ARRIVE). The prognosis of well-managed MI has improved greatly over the last 20 years[66]. Extended follow-up may now be required to determine whether possible reductions in non-fatal MI translate into a reduction in disability (heart failure) or death.

Modern approaches may help tailor treatment more precisely to an individual's risks and benefit. Coronary artery calcium scores combined with risk calculators may enable personalized risk stratification and identification of primary prevention adults who are at sufficiently high risk for CVD to potentially benefit from aspirin.[70,71] Risk scores need to be continually updated and validated to capture changes in demographics, smoking rates,[40,41] pharmacologic management of cardiovascular risk,[42] and obesity.[72]

Methods to mitigate the risk of bleeding may influence the risk/benefit ratio of aspirin. Along these lines, there is some interest in weight-based aspirin dosing,[73] though recent trials did not demonstrate effect modification by weight.[74] Different formulations of aspirin and enteric coating may reduce gastro-intestinal toxicity,[75] though this benefit must be weighed against potential reductions in antiplatelet effects with certain enteric-coated aspirin formulations.[76] The concomitant use of proton pump inhibitors reduces gastrointestinal bleeding events.[77,78] Compared with proton pump inhibitors, assessment and treatment of helicobacter pylori offers a similar degree of protection from recurrent bleeding among aspirin users.[79] Lifestyle modifications, such as minimizing NSAIDs and alcohol, might decrease gastrointestinal bleeding risk.[80] Finally, the use of bleeding risk scores specific to aspirin can inform decisions surrounding aspirin prescribing.[81]

The failure of recent trials of aspirin for primary prevention to demonstrate consistently a benefit for non-fatal and fatal CVD outcomes[27,28] should also lead to reassessment of its role in secondary prevention, particularly in the post-acute setting (i.e., greater than 1 year post MI/stroke/revascularization).[82] Indeed, intensive treatment of CVD risk factors may also have diminished the benefit of aspirin for secondary prevention among persons with stable CVD, though for now guidelines continue to recommend life-long aspirin for secondary prevention. A number of clinical trials have suggested that primary prevention aspirin might reduce the risk of developing cancer,[83,84] though ASPREE unexpectedly showed an increase in cancer deaths with aspirin. Longer follow up from all the recent trials will be necessary to shed further light on this issue,[85–87] and to guide aspirin prescription in specific patients with low hemorrhagic risk and high risk for both colon cancer and CVD.[88] Regardless, aspirin's cost-effectiveness for primary prevention was questionable even before the recent neutral trials.[89,90] Lastly, in an era with a growing number of CVD therapies and increasing complexity of care, withdrawal of aspirin therapy in primary prevention should be considered where appropriate.

In conclusion, aspirin does not reduce fatal cardiovascular events in patients who have not yet experienced a first event, but it does increase the risk of bleeding. However, case fatality from CVD has fallen dramatically in recent years so the potential importance of non-fatal endpoints must be borne in mind because aspirin still appears to reduce non-fatal MI, albeit less consistently and convincingly in contemporary trials. Thus, longer follow-up of recent pivotal trials will be important to see if aspirin might prevent heart failure and other morbid complications of MI over the longer term. Similarly, whether aspirin may have a role in preventing CVD in non-elderly adults who are higher risk than those studied in contemporary trials remains a dilemma and requires further study.

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JWM was responsible for the review concept with all authors contributing to its development. IR and CPM completed the literature search. IR, CPM, and JWM wrote the first draft of the manuscript. JWM, MV, DLB, DAW, JGFC, and RSB were responsible for critical appraisal and editing of the manuscript. All authors approved the final version.

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Table 1. Historic Randomized Control Trials for Aspirin in Primary Cardiovascular Prevention: Mid-enrollment Pre-2000. *fatal or nonfatal; BMI body mass index; CV cardiovascular; GI gastrointestinal; HLD hyperlipidemia; HTN hypertension; IHD ischemic heart disease; MI myocardial infarction; NR not reported; NS nonsignificant; PUD peptic ulcer disease; SBP systolic blood pressure

Trial	BMD	PHS	TPT	HOT	PPP	WHS
Year	1988	1989	1998	1998	2001	2005
Enrollment Period	1978-1979	1981-1987	1984-1989	1992-1994	1994-1998	1992-1995
Number of subjects	5139	22071	5085	18790	4495	39876
Population	Male physicians without history of MI, stroke, or PUD	Male physicians ages 40-84 without history of stroke, MI, cancer, or renal disease	Men ages 45-69 at high risk for cardiovascular disease	Men and women ages 50–80 with hypertension	Men and women ages ≥ 50 with one or more cardiovascular risk factors	Healthy women ages ≥ 45
Control Arm	no aspirin	placebo	placebo	placebo	no aspirin	placebo
Median Follow-up	5.5 years	5 years	6.8 years	3.8 years (mean)	4 years	10.1 years (mean)
Mean Age	47% age<60, 39% age 60-69, 14% age 70-79	41% age 40-49, 34% age 50-59, 19% age 60-69, 7% age 70-84	57 years	61 years	64 years	55 years
Current smoking	30%	11%	41%	16%	15%	13%
Hypertension	Mean SBP 136, 18% HTN	4% HTN	Mean SBP 139	Mean 170/105	Mean 145/85, 69% HTN	26%
Hyperlipidemia	NR	5% cholesterol ≥ 6.7 mmol/L	Mean 6.4 mmol/L	Mean 6.0 mmol/L	Mean 6.2 mmol/l, 41% HLD	30%
Statin use	NR	NR	NR	NR	16%	NR
Diabetes	2%	2%	NR	8%	17%	3%
Obesity	NR	25% BMI≥26	Mean BMI 27.4	Mean BMI 28.4	Mean BMI 27.5, obesity 22%	Mean BMI 26
Females	0%	0%	0%	47%	57%	100%
Dose of aspirin	300 or 500 mg	325 mg	75 mg	75 mg	100 mg	100 mg
Primary endpoint	CV Mortality (63.2 vs 62.3 per 10,000 man-years, p=NS)	CV Mortality (81 vs 83, RR 0.96 95% CI 0.6-1.54)	IHD (154 vs 190 events, p=0.04) IHD excluding warfarin arm (83 vs 107 events, p=NS)	Major CV events (315 vs 368, RR 0.85, 95% CI 0.73-0.99, p=0.03) not including silent MI	Major CV events (45 vs 64, RR 0.71, 95% CI 0.48-1.04)	Major CV events (477 vs 522, 0.91, 95% CI 0.80-1.03, p= 0.13)
Secondary endpoint	Nonfatal stroke (see below) and nonfatal MI (see below)	MI (139 vs 239, RR 0.56, 95% CI 0.45-0.70, p<0.00001); Stroke (119 vs 98, RR 1.22, 95% CI 0.93-1.60, p=0.15)	Stroke (47 vs 48, 2.9 vs 3.0 per 1000 man-years, p=NS)	MI (82 vs 127 RR 0.64 95% CI 0.49-0.85 p=0.002); Stroke (146 vs 148, RR 0.98, 95% CI 0.78-1.24, p=0.88); CV mortality (133 vs 140, RR 0.95, 95% CI 0.75-1.20, p=0.65)	Total CV events (141 vs 187, RR 0.77, 95% CI 0.62-0.95); CV death (17 vs 31, RR 0.56, 95% CI 0.31–0.99); all-cause mortality (see below)	Fatal MI (14 vs 12, RR 1.16, 95% CI 0.54-2.51, P = 0.70); Nonfatal MI (see below); Fatal stroke (23 vs 22, RR 1.04, 95% CI 0.58-1.86 p=0.90) Nonfatal stroke (see below); CV death (120 vs 126, RR 0.95, 95% CI 0.74-1.22; p= 0.68)
Safety endpoint	Extracranial bleeding (10.6 vs 7.4 per 10,000 man-years, p=NS)	Bleeding requiring transfusion (48 vs 28, RR 1.71, 95% CI 1.09 -2.69, p=0.02)	Major bleeding event (8 vs 4 p=NS) Intermediate bleeding event (48 vs 33 p=NS)	Fatal bleeds (7 vs 8, p=NS), Nonfatal major bleeds (129 vs 70, RR 1.8, p<0.001)	Severe bleeding (24 vs 6, p<0.0008)	GI bleeding req transfusion (127 vs 91, RR 1.40, 95% CI 1.07-1.83, p=0.02)
All-Cause Mortality	143.4 vs 159.5 per 10,000 man-years, p=NS	205 vs 216, RR 0.95, CI 0.79-1.15, p=0.60	216 vs 205, 13.0 vs 12.2 per 1000 man-years, p=NS	284 vs 305, RR 0.93, 95% CI 0.79-1.09, p=0.36	62 vs 78, RR 0.81, 95% CI 0.58-1.13	609 vs 642, RR 0.95, 95% CI 0.85-1.06, p=0.32
Nonfatal MI	42.5 vs 43.3 per 10,000 man-years, p=NS	129 vs 213, RR 0.59, 95% CI 0.47-0.74, p<0.00001	94 vs 137, 5.8 vs 8.5 per 1000 many-years, p=0.004	82 vs 127, RR 0.64, 95% CI 0.49-0.85, p=0.002*; 157 vs 184, RR 0.85, 95% CI 0.69-1.05, p=0.13* (including silent MI)	15 vs 22, RR 0.69, 95% CI 0.36-1.33	184-181, RR 1.01, 95% CI 0.83-1.24, p=0.90
Nonfatal Stroke	32.4 vs 28.5 per 10,000 man-years, p=NS	110 vs 92, RR 1.20, 95% CI 0.91 -1.59, p=0.20	47 vs 48, 2.9 vs 3.0 per 1000 man-years, p=NS*	146 vs 148, RR 0.98, 95% CI 0.78-1.24, p=0.88*	15 vs 18, RR 0.84, 95% CI 0.42-1.67	198 vs 244, RR 0.81, 95% CI 0.67-0.97, p=0.02

Table 2. Contemporary Randomized Control Trials for Aspirin in Primary Cardiovascular Prevention: Mid-enrollment Post-2000. *fatal or nonfatal; ABI ankle-brachial index; CV cardiovascular; DM Diabetes Mellitus; GI gastrointestinal; HLD hyperlipidemia; HTN hypertension; MI myocardial infarction; NR not reported; NS nonsignificant; SBP systolic blood pressure; TIA transient ischemic attack

Trial	POPADAD	JPAD	AAA	JPPP	ARRIVE	ASCEND	ASPREE
Year	2008	2008	2010	2014	2018	2018	2018
Enrollment Period	1997-2001	2002-2005	1998-2008	2005-2007	2007-2016	2005-2011	2010-2014
Number of subjects	1276	2539	3350	14464	12546	15480	19114
Population	Men and women ages ≥ 40 with DM and ABI ≤0.99	Men and women ages 30-85 with DM	Men and women ages 50-75 with ABI≤0.95	Men and women ages 60-85 with HTN, HLD, or DM	Men ages ≥ 55 with 2-4 CV risk factors; Women ages ≥ 60 with ≥ 3 CV risk factors	Men and women ages≥ 40 with DM	Men and women ages ≥ 70
Control Arm	placebo	no aspirin	placebo	no aspirin	placebo	placebo	placebo
Median Follow-up	6.7 years	4.4 years	8.2 years (mean)	5 years	5 years	7.4 years	4.7 years
Mean Age	61 years	65 years	62 years	71 years	64 years	63 years	74 years (median)
Current Smoking	31%	21%	33%	13%	29%	8%	4%
Hypertension	Mean 145/79	Mean 135/77 58% HTN	Mean 148/84	Mean 137/78, 85% HTN	Median SBP 145, 63% HTN	Mean SBP136, 29% HTN,	Mean 139/77, 74% HTN
Hyperlipidemia	Mean 5.5 mmol/l	Mean 5.2 mmol/l 53% HLD	Mean 6.2 mmol/l	Mean 5.2 mmol/l 72% HLD	58% HLD	Mean 4.2 mmol/l 34% HLD	Mean 5.2 mmol/l 65% HLD
Statin use	NR	26%	4% increased to 25%	NR	43%	75%	34%
Diabetes	100%	100%	3%	34%	0%	100%	11%
Obesity	Mean BMI 29.3	Mean BMI 24	NR	Mean BMI 24.2, 36% BMI>25	Mean BMI 28.4, 79% BMI >25	Mean BMI 31, 85% BMI >25	30% BMI>30
Females	56%	44%	72%	58%	30%	27%	56%
Dose of aspirin	100 mg	81 or 100 mg	100 mg	100 mg	100 mg	100 mg	100 mg
Primary endpoint	Major CV events (116 vs 117, RR 0.98, 95% CI 0.76-1.26, p=0.86); CV death (43 vs 35, RR 1.23, 95% CI 0.79-1.93, p=0.36)	Major CV events (68 vs 86, RR 0.80, 95% CI 0.58-1.10, p=0.16)	Major CV events (13.7 vs 13.3 per 1000 person-years, RR 1.03, 95% CI 0.84-1.27)	Major CV events (193 vs 207, RR 0.94, 95% CI 0.77-1.15, p=0.54)	Major CV events (269 vs 281, RR 0.96, 95% CI 0.81–1.13, p=0.60)	Major CV events (658 vs 743, RR 0.88, 95% CI 0.79-0.97, p=0.01)	Death, dementia, or persistent physical disability (21.5 vs 21.2 per 1000 person-years, RR 1.01, 95% CI 0.92-1.11, p=0.79)
Secondary endpoint	All-cause mortality (see below); non-fatal myocardial infarction (see below); Other vascular events (not included)	CV mortality (1 vs 10, RR 0.10, 95% CI 0.01-0.79 p=0.0037); CHD events (28 vs 35, RR 0.81, 95% CI 0.49-1.33, p=0.40); nonfatal MI or stroke, all-cause mortality	Composite of primary end point or angina, claudication, or TIA (22.8 vs 22.9 per 1000 person-years, RR 1.00, 95% CI, 0.85-1.17) and all-cause mortality (see below)	Composite of primary endpoint or atherosclerosis (280 vs 319, RR 0.89 95% CI 0.75-1.04 p=0.14), CV death (58 vs 57, RR 1.03, 95% CI 0.71-1.48, p=0.89)	Composite and individual outcomes of the time to CV death, MI, or stroke. Time to UA; time to TIA; and time to death (p=NS for all endpoints)	Any major vascular event (833 vs 936, RR 0.88, 95% CI 0.80-0.97); GI cancer (157 vs 158, RR 0.99, p=NS)	Major CV events (10.7 events vs 11.3 per 1000 person-years, RR 0.95, 95% CI 0.83-1.08)
Safety endpoint	GI bleeding (28 vs 31, RR 0.90, 95% CI 0.53-1.52, p=0.69)	Hemorrhagic stroke or severe GI bleeding (10 vs 7 p=NS)	Major hemorrhage req hospitalization (34 vs 20, RR 1.71, 95% CI 0.99-2.97)	Extracranial bleed req transfusion or hospital (62 vs 34, RR 1.85, 95% CI 1.22-2.81, p=0.004)	GI bleeding events (61 vs 29, RR 2.11, 95% CI 1.36–3.28, p=0.0007)	Major bleeding event (314 vs 245, RR 1.29, 95% CI, 1.09-1.52, P=0.003)	Major hemorrhage (8.6 vs 6.2 per 1000 person-years, RR 1.38, 95% CI 1.18-1.62, P<0.001)
All-Cause Mortality	94 vs 101, RR 0.93, 95% CI 0.71-1.24, p=0.63	34 vs 38, RR 0.90, 95% CI 0.57-1.14, p=0.67	176 vs 186, RR 0.95, 95% CI 0.77-1.16	297 vs 303, RR 0.99 95% CI, 0.85-1.17, p=0.93	160 vs 161, RR 0.99, 95% CI 0.80–1.24, p=0.95	748 vs 792, RR 0.94, 95% CI 0.85-1.04	12.7 vs 11.1 per 1000 person-years, RR 1.14, 95% CI 1.01 to 1.29
Nonfatal MI	55 vs 56, RR 0.98, 95% CI 0.68-1.43, p=0.93	12 vs 9, RR, 1.34 95% CI 0.57-3.19, p=0.50	62 vs 68 p=NS	20 vs 38, RR 0.53, 95% CI 0.31-0.91, P = 0.02	88 vs 98, RR 0.90, 95% CI 0.67-1.20, p=0.46	191 vs 195, RR 0.98, 95% CI 0.80–1.19	171 vs 184, RR 0.93, 95% CI 0.76-1.15*
Nonfatal Stroke	29 vs 41, RR 0.71, 95% CI 0.44 to 1.14, p=0.15	22 vs 24, RR 0.93, 95% CI 0.52-1.66, p=0.80	37 vs 38 p=NS	117 vs 114, RR 1.04, 95% CI 0.80-1.34, p=0.78	75 vs 67, RR 1.12, 95% CI 0.8-1.55, p=0.51*	202 vs 229, RR 0.88, 95% CI 0.73-1.06	148 vs 167, RR 0.89, 95% CI 0.71-1.11*

Table 3. Cardiovascular Risk Burden and Statin Use in Historic and Contemporary Trials

	Pre-2000 weighted average	Trials included	Post-2000 weighted average	Trials included
Smoking (%)	15.6	BMD, PHS, TPT, HOT, PPP, WHS	13.9	POPADAD, JPAD, AAA, JPPP, ARRIVE, ASCEND, ASPREE
HTN (average SBP)	157	BMD, TPT, HOT, PPP	140	POPADAD, JPAD, AAA, JPPP, ARRIVE, ASCEND, ASPREE
DM (%)	4.4	BMD, PHS, HOT, PPP, WHS	38.4	POPADAD, JPAD, AAA, JPPP, ARRIVE, ASCEND, ASPREE
Obesity (average BMI)	26.9	TPT, HOT, PPP, WHS	27.7	POPADAD, JPAD, JPPP, ARRIVE, ASCEND
Cholesterol (average mmol/L)	6.1	TPT, HOT, PPP	5.0	POPADAD, JPAD, AAA, JPPP, ASCEND, ASPREE
Statin use (%)	16	PPP	47	JPAD, AAA, ARRIVE, ASCEND, ASPREE

Table 4. Definitions of Nonfatal Myocardial Infarction: *Cardiac enzymes during this time were SGOT, CK, LDH

Trial	Definition of Nonfatal Myocardial Infarction
BMD	Self-reported myocardial infarctions which were confirmed by cardiologist or neurologist review and classified as "definite", "probable", or "doubtful" event, with "doubtful" events removed from the analysis
PHS	World Health Organization criteria (1971) 1) ECG with unequivocal changes or 2) Atypical or typical symptoms with equivocal ECG and elevated enzymes* or 3) Typical history and elevated enzymes* with ECG negative or not available
TPT	World Health Organization criteria (1976)
HOT	At least 2 of 3 1. Central chest pain lasting for more than 15 min 2. Transient elevation of enzymes* indicating myocardial damage 3. Typical ECG changes
PPP	At least 2 of 3 1. Chest pain of typical intensity and duration 2. Transient increase of serum enzymes* concentration indicating myocardial damage 3. Typical ECG changes
WHS	Symptoms met World Health Organization criteria and if the event was associated with abnormal levels of cardiac enzymes* or diagnostic ECG
POPADAD	Definition according to the World Health Organization criteria
JPAD	Not reported
AAA	American Heart Association Criteria (Gillum 1984) 1. Evolving diagnostic ECG and/or 2. Diagnostic ECG and abnormal enzymes (CK, CKMB, SGOT, LDH) and/or 3. Prolonged cardiac pain and abnormal enzymes (CK, CKMB, SGOT, LDH)
JPPP	European Society of Cardiology and American College of Cardiology Criteria (Luepker 2003) 1. Evolving diagnostic ECG, or 2. Diagnostic biomarkers (CK, CK-MB, CK-Mbm, or cTn)
ARRIVE	At least 2 of 3 1. A consistent clinical history 2. ECG consistent with ischemia 3. Cardiac biomarkers elevation
ASCEND	Evidence of cardiac necrosis (cardiac biomarkers) and evidence of acute MI (symptoms, new ECG changes, imaging or angiography)
ASPREE	European Society of Cardiology and the American College of Cardiology Criteria (Alpert 2000) 1) Rise and fall of biomarkers (CK-MB or troponin) with at least one of the following: a) Ischemic symptoms b) Development of pathologic Q waves on the ECG c) ECG changes indicative of ischemia (ST segment elevation or depression) d) coronary artery intervention

Table 5. Summary of Major International Guidelines on Aspirin in Primary Cardiovascular Prevention

Year	Guideline	Recommendation
2002	USPSTF	Consider use of aspirin with adults at risk for coronary heart disease (5-year risk over 3%)
2002	AHA	Consider use of aspirin with adults 10% or more 10-year risk of cardiovascular disease
2007	ESC	Consider use of aspirin when the 10-year risk of cardiovascular mortality is significantly increased (SCORE risk>10%) and blood pressure is controlled
2009	USPSTF	Recommend aspirin for men ages 45 to 79, and women ages 55 to 79 when cardiovascular benefit outweighs the risk of bleed (Grade A)
2015	AHA/ADA	Recommend aspirin for DM patients who have a 10-year CVD risk of at least 10% but are not at increased risk of bleeding (Class IIa). Aspirin is reasonable for adults who have DM and a 10-year CVD risk between 5% and 10% (Class IIb)
2016	USPSTF	Recommend aspirin in patients aged 50-59 with a 10% or greater 10-year CVD risk and low risk of bleeding (Grade B)
2016	ESC	Recommend against initiating aspirin in individuals without overt cardiovascular disease

Figure Legend:
Figure illustrating the history of aspirin for use in the primary prevention of cardiovascular disease including major completed trials, FDA reviews, and international practice guidelines.